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Synthesis and biological activity of apratoxin derivatives

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ABSTRACT

This review covers the total asymmetric synthesis and biological evaluation of derivatives of the marine natural products known as the apratoxins.

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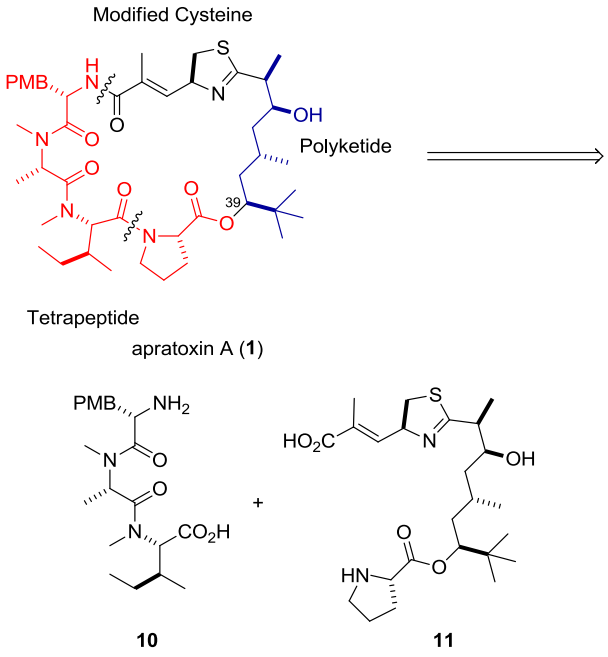
1. Introduction

Natural products have proven to be an abundant source of inspiration for anticancer drugs. Both natural products and natural product-related compounds account for approximately three-quarters of the anticancer drugs currently on the global market.[1] The apratoxin family, consisting of apratoxins A-H and apratoxin A sulfoxide (**1**–**9**, Fig. 1), is a group natural products isolated from the *Lyngbya* species of cyanobacteria.[2–7] Members of the apratoxin family have shown to exhibit strong cytotoxicity against various cancer cell lines, often at low nM concentrations. Structurally, the apratoxins can be described as cyclic depsipeptides comprised of a polyketide and a polypeptide domain. The nine members of the apratoxin family have been discovered over the course of the past 16 years. The first of which, apratoxin A, was isolated in 2001 by Moore, Paul and co-workers.[2] Since this time, the apratoxin family has garnered much attention from the synthetic community due the potent antiproliferative activity as well as the synthetically challenging molecular architecture. The first total synthesis of apratoxin A was completed by Chen and Forsyth in 2003.[8,9] Additional total syntheses of apratoxin A and other members of the apratoxin family have recently been reviewed.[10] The scope of this review will cover the asymmetric total synthesis of structural derivatives of the apratoxin family and the study of their biological activity.



Scheme 1. General retrosynthesis of the apratoxins.

2. General retrosynthesis of apratoxin derivatives

Researchers have diversified the modification sites of the parent compound, apratoxin A, to include changes in the thiazoline moiety, the polypeptide and polyketide moieties, and to construct apratoxin hybrids. The retrosynthesis of the derivatives presented are generally similar. The apratoxin framework can be divided into three regions: a modified cysteine residue, a polyketide group containing four stereogenic centers, and a tetrapeptide containing *O*-Me-Tyr, *N*-Me-Ala, *N*-Me-Ile, and proline (Scheme 1). However, in the reported syntheses of the naturally occurring apratoxins and the derivatives, as shown in this review, the syntheses of the apratoxin framework is broken into 2 fragments: a tripeptide unit made up of *O*-Me-Tyr, *N*-Me-Ala, and *N*-Me-Ile (**10**) and a proline and modified cysteine residue containing polyketide moiety (**11**). This strategy has been used in anticipation of a higher yielding peptide coupling between proline and *N*-Me-Ile, rather than ester formation between a tetrapeptide containing proline and a hindered C-39 alcohol of the polyketide. While the synthesis of tripeptide **10** is relatively straightforward using standard peptide coupling, the synthesis of polyketide **11** is the more challenging aspect of the total syntheses presented.

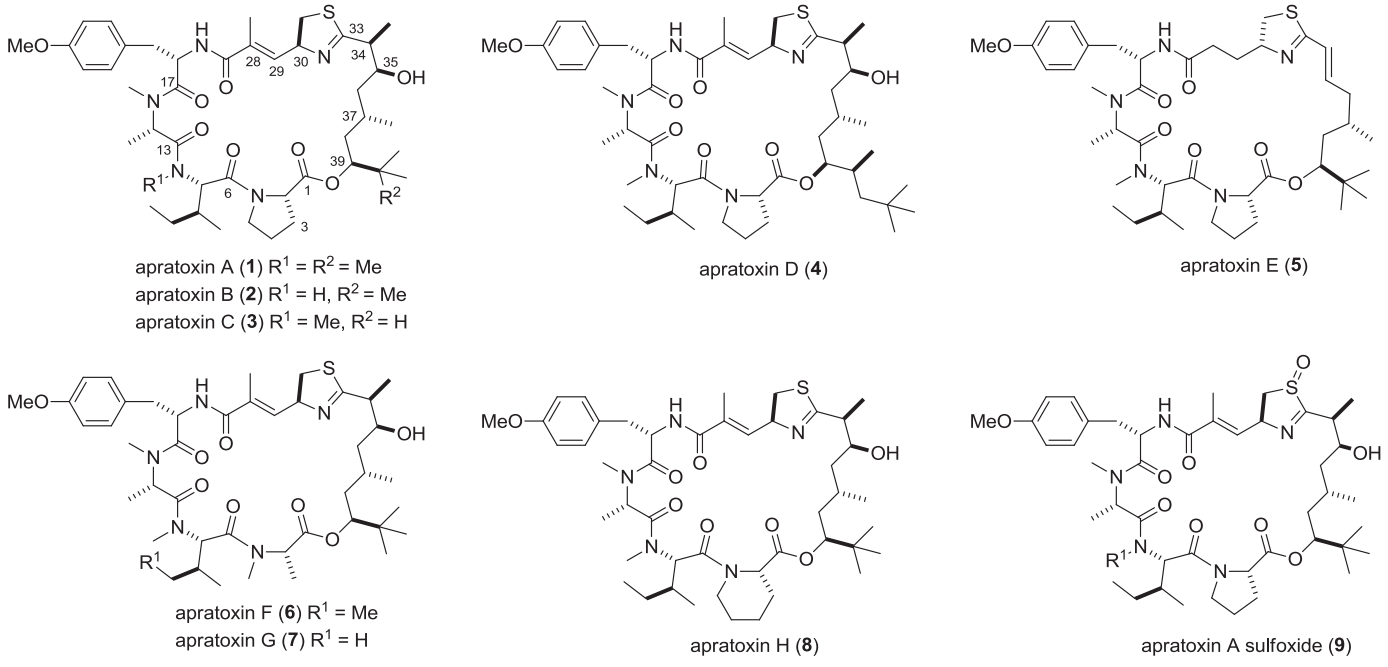


Fig. 1. The apratoxins.

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